

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
25 November 2004 (25.11.2004)

PCT

(10) International Publication Number
WO 2004/101072 A1

(51) International Patent Classification⁷: A61P 25/00,
23/00, A61K 39/395, 31/00, G01N 33/48

(21) International Application Number:
PCT/CA2004/000726

(22) International Filing Date: 14 May 2004 (14.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/470,885 16 May 2003 (16.05.2003) US

(71) Applicant (for all designated States except US): UNI-
VERSITE LAVAL [CA/CA]; Cité Universitaire, Québec,
Québec G1K 7P4 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): DE KONINCK,
Yves [CA/CA]; 3770 Le Corbusier, Ste Foy, Québec G1W
4P4 (CA). DE KONINCK, Paul [CA/CA]; 1285 de la
Monnerie, Cap Rouge, Québec G1Y 1P5 (CA). COULL,
Jeffrey [CA/CA]; 26 rue Garneau, Apt. 5, Québec,
Québec G1R 3V2 (CA).

(74) Agent: SMART & BIGGAR; Suite 3400, 1000 de la
Gauchetière Street West, Montreal, Quebec H3B 4W5
(CA).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

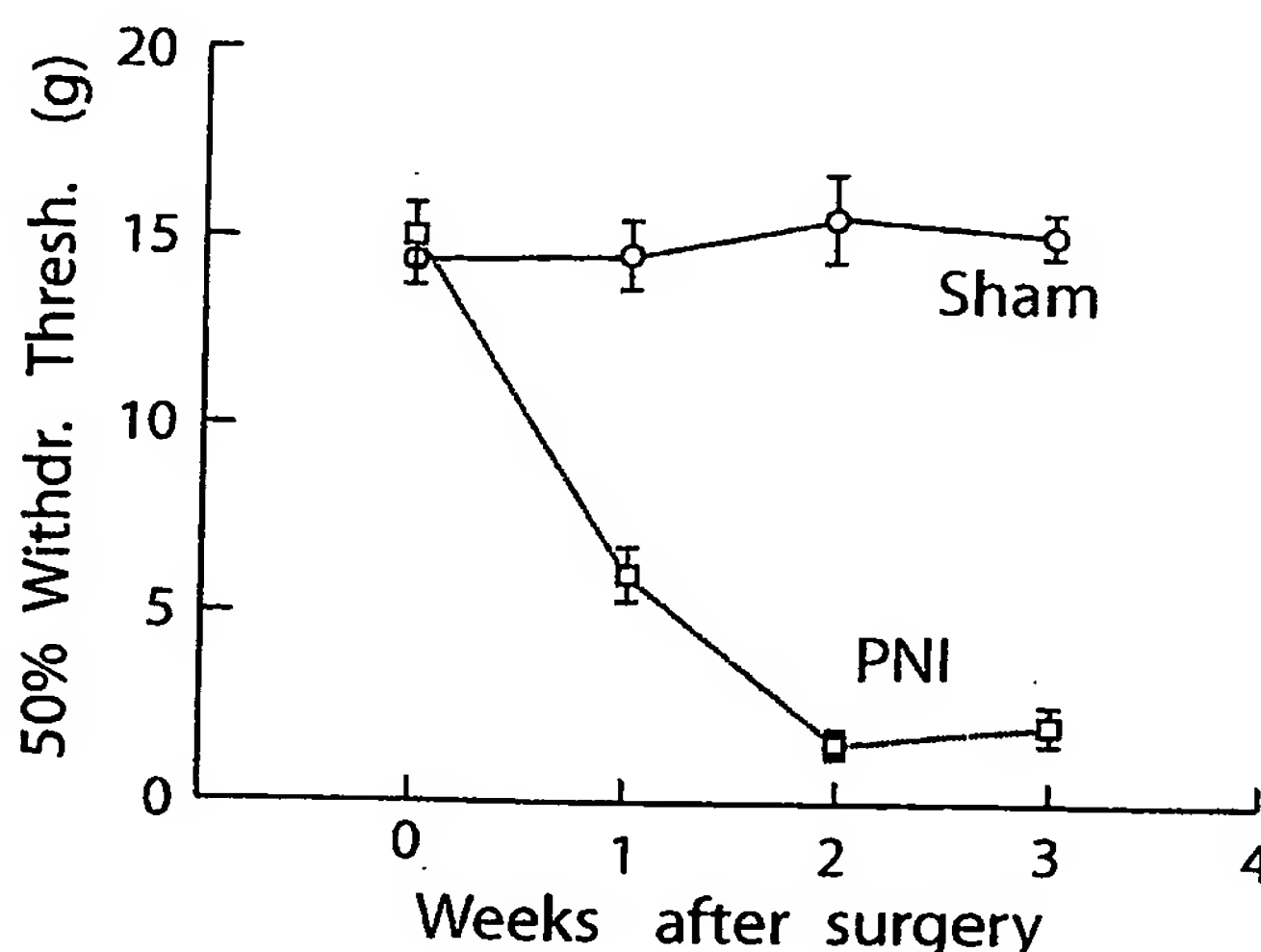
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: CNS CHLORIDE MODULATION AND USES THEREOF



(57) Abstract: Methods and products for the attenuation
or treatment of pain and the reduction of nociception
are described. The methods and products are based on
the modulation of CNS intracellular chloride levels. The
methods and products may also relate to modulation of
the activity and/or expression of a chloride transporter,
such as the KCC2 potassium-chloride cotransporter.
Also described herein are commercial packages and
uses based on such modulation. Related methods for
identifying or characterizing a compound for the treatment
of pain, the reduction of nociception and the diagnosis and
prognostication of pain are also described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA2004/000726

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61P25/00 A61P23/00 A61K39/395 A61K31/00 G01N33/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, MEDLINE, EMBASE, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
------------	--	-----------------------

X	<p>US 2002/028779 A1 (HIGH KARIN WESTLUND ET AL) 7 March 2002 (2002-03-07)</p> <p>paragraph '0010! - paragraph '0012! paragraph '0023! paragraph '0028! - paragraph '0029! paragraph '0041! paragraph '0050! - paragraph '0051! example 2 claims 4,12,19</p> <p style="text-align: center;">----- -/-</p>	<p>1-16, 21-39, 53-59,64</p>
---	---	--------------------------------------

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

23 September 2004

Date of mailing of the international search report

08/10/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Irion, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA2004/000726

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 02/102232 A (UNIV CALIFORNIA ; LEVINE JON DAVID (US); MESSING ROBERT O (US)) 27 December 2002 (2002-12-27)</p> <p>page 7, line 4 - line 8 page 3, line 1 - line 2 page 10, line 20 - line 23 page 14, line 7 - line 9 page 56, line 17 - line 20 claim 94</p>	<p>1-13,17, 18, 21-37, 40,41, 53-57, 60,61,64</p>
X	<p>-----</p> <p>ALEY KOCHUVELIKAKAM O ET AL: "Role of protein kinase A in the maintenance of inflammatory pain" JOURNAL OF NEUROSCIENCE, vol. 19, no. 6, 15 March 1999 (1999-03-15), pages 2181-2186, XP002297725 ISSN: 0270-6474 abstract</p>	<p>1-13,17, 18, 21-37, 40,41, 53-57, 60,61,64</p>
X	<p>-----</p> <p>HUA XIAO-YING ET AL: "Inhibition of spinal protein kinase C reduces nerve injury-induced tactile allodynia in neuropathic rats" NEUROSCIENCE LETTERS, vol. 276, no. 2, 3 December 1999 (1999-12-03), pages 99-102, XP002297726 ISSN: 0304-3940 abstract</p>	<p>1-13,17, 18, 21-37, 40,41, 53-57, 60,61,64</p>
X	<p>-----</p> <p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2001, FANG L ET AL: "CaMK II signaling in central sensitization in a rat model of visceral pain" XP002297727 Database accession no. PREV200200002912 abstract & SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 2, 2001, page 2163, 31ST ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE; SAN DIEGO, CALIFORNIA, USA; NOVEMBER 10-15, 2001 ISSN: 0190-5295</p> <p>-----</p>	<p>1-7,9, 11-13, 19-37, 42,43, 53-57, 62-64</p>

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA2004/000726

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/032870 A (RINAT NEUROSCIENCE CORP ; SHELTON DAVID L (US); VERGARA GERMAN J (US)) 22 April 2004 (2004-04-22) paragraph '0042!; figure 9 paragraph '0128! paragraph '0185!; example 5	1-16, 21-39, 53-59,64
P,X	COULL JEFFREY A M ET AL: "Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain." NATURE (LONDON), vol. 424, no. 6951, 21 August 2003 (2003-08-21), pages 938-942, XP002294556 ISSN: 0028-0836 the whole document	44-52, 65-81
P,A	----- WO 93/00909 A (REGENERON PHARMA) 21 January 1993 (1993-01-21) the whole document	1-43, 53-64
A	----- WO 01/85151 A (RAYCHAUDHURI SIBA P ; RAYCHAUDHURI SMRITI K (US); FARBER EUGENE M (US)) 15 November 2001 (2001-11-15) the whole document	1-16, 21-39, 53-59,64
A	----- DE PLATER G M ET AL: "Venom from the platypus, Ornithorhynchus anatinus, induces a calcium-dependent current in cultured dorsal root ganglion cells" JOURNAL OF NEUROPHYSIOLOGY (BETHESDA), vol. 85, no. 3, March 2001 (2001-03), pages 1340-1345, XP002294557 ISSN: 0022-3077 the whole document	1-16, 21-39, 53-59,64

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/000726

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-21, 31, 33, 35-43, 53-81 (all partially)
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of Box II.1

Although claims 1-21,31,33,35-43,53-81 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 65-81 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2002028779	A1	07-03-2002	NONE	
WO 02102232	A	27-12-2002	WO 02102232 A2	27-12-2002
			US 2003008807 A1	09-01-2003
WO 2004032870	A	22-04-2004	WO 2004032870 A2	22-04-2004
WO 9300909	A	21-01-1993	AU 2322392 A	11-02-1993
			CA 2112799 A1	21-01-1993
			EP 0593663 A1	27-04-1994
			IE 921315 A1	13-01-1993
			JP 6509333 T	20-10-1994
			NZ 242467 A	27-06-1995
			PT 100424 A	29-10-1993
			WO 9300909 A1	21-01-1993
			ZA 9202946 A	30-12-1992
WO 0185151	A	15-11-2001	AU 6132401 A	20-11-2001
			WO 0185151 A2	15-11-2001